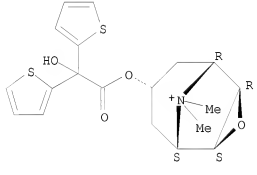
L2 ANSWER 22 OF 23 REGISTRY COPYRIGHT 2009 ACS on STN
RN 136310-93-5 REGISTRY
ED Entered STN: 20 Sep 1991
CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane,
    7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1),
    (1α,2β,4β,5α,7β)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 3-Oxa-9-azatricyclo[3.3.1.02,4]nonane,
    3-oxa-9-azoniatricyclo[3.3.1.02,4]nonane deriv.
CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane,
    7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide,
    (1α,2β,4β,5α,7β)- (9CI)
OTHER NAMES:
CN (1α,2β,4β,5α,7β)-7-[(Hydroxydi-2-
    thienylacetyl)oxy]-9,9-di-methyl-3-oxa-9-azoniatricyclo[3.3.1.0]nonane
    bromide
CN BA 679BR
CN Spiriva
CN tiopropium
CN **Tiotropium bromide**
FS STEREOSEARCH
MF C19 H22 N O4 S2 . Br
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS,
      CASREACT, CHEMCATS, CIN, CSCHEM, EMBASE, IMSCOSEARCH, IMSDRUGNEWS,
      IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PATDPASPC,
      PHAR, PIRA, PROMT, PROUSDDR, PS, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
        (*File contains numerically searchable property data)
CRN (186691-13-4)

Relative stereochemistry.



● Br⁻

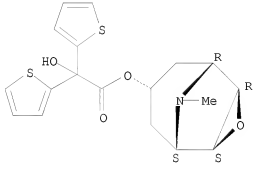
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

267 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
267 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 23 OF 23 REGISTRY COPYRIGHT 2009 ACS on STN
RN 136310-64-0 REGISTRY

ED Entered STN: 20 Sep 1991
CN 2-Thiopheneacetic acid, α-hydroxy-α-2-thienyl-,
    (1α,2β,4β,5α,7β)-9-methyl-3-oxa-9-
    azatricyclo[3.3.1.02,4]non-7-yl ester (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 2-Thiopheneacetic acid, α-hydroxy-α-2-thienyl-,
    9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl ester,
    (1α,2β,4β,5α,7β)-
CN 3-Oxa-9-azatricyclo[3.3.1.02,4]nonane, 2-thiopheneacetic acid deriv.
OTHER NAMES:
CN Di(2-thienyl)glycolic acid scopine ester
CN **N-Demethyl tiotropium**
CN Scopine di(2-thienylglycolate)
FS STEREOSEARCH
MF C18 H19 N O4 S2
CI COM
SR CA
LC STN Files: CA, CAPLUS, CASREACT, CHEMCATS, PS, USPAT2, USPATFULL

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 136310-93-5
L3 1 136310-93-5
    (136310-93-5/RN)

=> file caplus
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION
FULL ESTIMATED COST 64.64 70.14

FILE 'CAPLUS' ENTERED AT 22:29:07 ON 27 MAR 2009
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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FILE COVERS 1907 - 27 Mar 2009 VOL 150 ISS 14
FILE LAST UPDATED: 26 Mar 2009 (20090326/ED)

Caplus now includes complete International Patent Classification (IPC) reclassification data for the third quarter of 2008.

CAS Information Use Policies apply and are available at:

http://www.cas.org/legal/infopolicy.html

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3 <> or tiotropium?

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.50	70.64

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L4 SEL L3 1- CHEM : 6 TERMS

SET SMARTSELECT OFF
SET COMMAND COMPLETED

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	15.08	85.72

FILE 'CAPLUS' ENTERED AT 22:29:24 ON 27 MAR 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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S L4 OR TIOTROPIUM?

511 TIOTROPIUM?
L6 523 L5 OR TIOTROPIUM?

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=> s l6 and (bladder or urinary or incontinence or urgency or urogenital)
         43327 BLADDER
          2626 BLADDERS
         43788 BLADDER
                 (BLADDER OR BLADDERS)
        138586 URINARY
          5721 INCONTINENCE
             2 INCONTINENCES
          5722 INCONTINENCE
                 (INCONTINENCE OR INCONTINENCES)
          1209 URGENCY
            25 URGENCIES
          1225 URGENCY
                 (URGENCY OR URGENCIES)
          4511 UROGENITAL
             1 UROGENITALS
          4512 UROGENITAL
                 (UROGENITAL OR UROGENITALS)
L7          18 L6 AND (BLADDER OR URINARY OR INCONTINENCE OR URGENCY OR UROGENI
               TAL)

=> focus
PROCESSING COMPLETED FOR L7
L8           18 FOCUS L7 1-

=> d ibib abs hist 1-18
'IBIB' IS NOT VALID HERE
For an explanation, enter "HELP DISPLAY HISTORY".

=> d ibib abs hitstr 1-18

L8   ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         2008:1445323  CAPLUS
DOCUMENT NUMBER:          150:90183
TITLE:                    Tiotropium does not affect lower
                          urinary tract functions in COPD patients with
                          benign prostatic hyperplasia
AUTHOR(S):                Miyazaki, Hiroo; Suda, Takafumi; Otsuka, Atsushi;
                          Nagata, Masao; Ozono, Seiichiro; Hashimoto, Dai;
                          Nakamura, Yutaro; Inui, Naoki; Nakamura, Hirotoshi;
                          Chida, Kingo
CORPORATE SOURCE:         Second Division, Department of Internal Medicine,
                          Hamamatsu University School of Medicine, 1-20-1
                          Handayama, Higashi-ku, Hamamatsu, Shizuoka, 431-3192,
                          Japan
SOURCE:                   Pulmonary Pharmacology & Therapeutics (2008), 21(6),
                          879-883
                          CODEN: PPTHFJ; ISSN: 1094-5539
PUBLISHER:                Elsevier Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Background: Tiotropium is widely used for the treatment of
     chronic obstructive pulmonary disease (COPD), but it is not usually
     prescribed for patients with micturition disorder, such as benign
     prostatic hyperplasia (BPH), because of the potential to increase the risk
     of acute urinary retention through its anticholinergic effects.
     However, no data are available to prove a true causal relation between
     tiotropium and lower urinary tract dysfunction (LUTD)
     using quant. symptomatic scoring or objective parameters evaluated by
     uroflowmetry.  Objective: To clarify the effect of tiotropium on
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lower **urinary** tract functions in COPD patients with BPH. Methods: This prospective pilot study comprised 25 male COPD patients with BPH as defined by the International Prostate Symptom Score (IPSS), the quality of life (QOL) index, maximum flow rate (Q-max) in uroflowmetry, and prostate volume Patients were given **tiotropium** once a day for 3 mo. At baseline and after treatment, lower **urinary** tract functions were assessed symptomatically by the IPSS and the QOL index, and objectively by **urinary** parameters, including Q-max, average flow rate (Q-ave), postvoid residual urine volume (PVR), and **bladder** voiding efficiency (BVE). Results: Acute **urinary** retention was not observed in any patients. Subjectively, no significant difference was found in the IPSS or the QOL index between baseline and after **tiotropium** treatment. Addnl., **tiotropium** treatment did not change Q-max, Q-ave, time to Q-max, or overall flow time compared to baseline (Q-max (mL/s), 9.66±3.63, 9.11±3.68 and 10.51±3.88, P=0.15; Q-ave (mL/s), 4.20±1.76, 4.14±1.55, and 4.71±1.81, P=0.31; time to Q-max (s), 12.1±8.0, 16.2±11.4, and 13.0±11.3, P=0.10; flow time (s), 39.4±19.6, 40.4±20.1, and 38.3±19.1; baseline, 1 mo after treatment and 3 mo after treatment, resp.). No significant increase was found in PVR or BVE (PVR (mL), 57.9±51.2, 55.4±47.2 and 66.1±52.7, P=0.36; BVE (%), 75.8±18.4, 73.3±19.1 and 73.9±17.3, P=0.67; baseline, 1 mo after treatment, and 3 mo after treatment, resp.). Conclusion: In our preliminary study, **tiotropium** did not adversely affect lower **urinary** tract functions in COPD patients with BPH, suggesting the possibility that **tiotropium** can be safely given to those patients. This warrants future studies in a larger series of COPD patients to validate our observations.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:209215 CAPLUS
DOCUMENT NUMBER: 144:280585
TITLE: Medicaments for the treatment of **urinary** tract disorders comprising anticholinergic agents
INVENTOR(S): Pieper, Michael P.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
SOURCE: Eur. Pat. Appl., 36 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1632229	A1	20060308	EP 2004-19003	20040811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
PRIORITY APPLN. INFO.:			EP 2004-19003	20040811

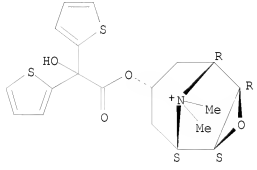
OTHER SOURCE(S): MARPAT 144:280585
AB The present invention relates to the use of one or more, preferably one long acting anticholinergic for the preparation of a medicament for oral, parenteral, or topical administration for the treatment of **urinary** tract disorders, such as **incontinence**. For example, a solution for injection contained tropenol 2,2-diphenylpropionic acid ester methobromide 1.7 mg, Me 4-hydroxybenzoate 18 mg, Pr 4-hydroxybenzoate 2 mg, NaCl 60 mg and water to 10 mL.
IT **136310-93-5, Tiotropium bromide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(compns. containing anticholinergic agent for treatment of **urinary** tract disorders)

RN 136310-93-5 CAPLUS

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:93067 CAPLUS

DOCUMENT NUMBER: 146:308973

TITLE: Pooled clinical trial analysis of **tiotropium** safety

AUTHOR(S): Kesten, Steven; Jara, Michele; Wentworth, Charles; Lanes, Stephan

CORPORATE SOURCE: Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA

SOURCE: Chest (2006), 130(6), 1695-1703
CODEN: CHETBF; ISSN: 0012-3692

PUBLISHER: American College of Chest Physicians

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Background: Marketing approval of pharmaceutical products is often based on data from several thousand subjects or fewer. Evaluation of safety is greatly enhanced by augmenting the safety database with postapproval studies. Methods: We conducted a pooled anal. of adverse event data from 19 randomized, double-blind, placebo-controlled trials with **tiotropium** in patients with obstructive lung disease. We computed incidence rates and rate ratios (RRs) for various reported adverse event end points of interest. Patients contributed person-time to the anal. as long as they were in the study until 30 days after treatment (**tiotropium**, placebo), or until they had the event of interest, whichever came first. Studies were pooled using the Mantel-Haenszel estimator, and we used 95% confidence intervals (CIs) to assess the precision of effect ests. Results: The pooled trial population includes 4,435 **tiotropium** patients and 3,384 placebo patients contributing 2,159 person-years of exposure to **tiotropium** and 1,662 person-years of exposure to placebo. Dyspnea, dry mouth, COPD exacerbation, and upper respiratory tract infection were the most commonly

reported events. There was a higher relative risk of dry mouth in the **tiotropium** group (RR, 3.60; 95% CI, 2.56 to 5.05). There was a lower risk of dyspnea (RR, 0.64; 95% CI, 0.50 to 0.81) and COPD exacerbation (RR, 0.72; 95% CI, 0.64 to 0.82) in patients receiving **tiotropium** compared to patients receiving placebo. Other results of interest are as follows: (1) all-cause mortality (RR, 0.76; 95% CI, 0.50 to 1.16); (2) cardiovascular mortality (RR, 0.57; 95% CI, 0.26 to 1.26); and (3) respiratory mortality (RR, 0.71; 95% CI, 0.29 to 1.74). The relative risk of **urinary** retention was 10.93 (95% CI, 1.26 to 94.88). Conclusions: Pooling of adverse event data from preapproval and postapproval **tiotropium** clin. trials increase the precision of effect ests. and supports the present safety profile of **tiotropium**.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

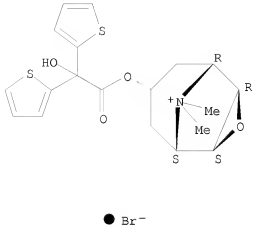
ACCESSION NUMBER: 2007:956388 CAPLUS
DOCUMENT NUMBER: 147:397551
TITLE: Role of **tiotropium** in the treatment of COPD
AUTHOR(S): Rice, Kathryn L.; Kunisaki, Ken M.; Niewoehner, Dennis E.
CORPORATE SOURCE: University of Minnesota, Minneapolis, MN, USA
SOURCE: International Journal of Chronic Obstructive Pulmonary Disease (2007), 2(2), 95-105
CODEN: IJCOC3; ISSN: 1176-9106
PUBLISHER: Dove Medical Press (NZ) Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. **Tiotropium** is a potent, long-acting, selective anticholinergic bronchodilator. Treatment with **tiotropium** produces sustained improvements in lung function, particularly FEV1 (peak, trough, average, and area under the curve) compared with either placebo or ipratropium in patients with moderate to severe COPD. Preliminary evidence suggests that treatment with **tiotropium** may slow the rate of decline in FEV1, but this finding awaits confirmation. **Tiotropium** reduces lung hyperinflation, with associated improvements in exercise capacity. **Tiotropium**, compared with either placebo or ipratropium, improves a variety of patient-centered outcomes, including subjective dyspnea ratings and HRQL scores. **Tiotropium** reduces the frequency of COPD exacerbations and of hospitalizations due to exacerbations, but has not been shown to reduce all-cause mortality. Compared with the long-acting bronchodilators, **tiotropium** provides incrementally better bronchodilation, but it is not clearly superior in terms of patient-centered outcomes. **Tiotropium** has a good safety profile; however patients with severe cardiac disease, **bladder** outlet obstruction, or narrow angle glaucoma were excluded from all studies. Medico economic analyses suggest that treatment with **tiotropium** may also be cost-effective, primarily by reducing costs associated with hospitalizations.

IT **136310-93-5**, **Spiriva**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**Spiriva** was effective than Atrovent in improving lung function, decline in forced expiratory volume, dyspnea and was safe and cost-effective in patient with chronic obstructive pulmonary disease)

RN 136310-93-5 CAPLUS
CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:122491 CAPLUS
DOCUMENT NUMBER: 148:322597
TITLE: A dose-ranging study of **tiotropium** delivered via Respimat Soft Mist Inhaler or HandiHaler in COPD patients
AUTHOR(S): Caillaud, Denis; Le Merre, Charles; Martinat, Yan; Aguilaniu, Bernard; Pavia, Demetri
CORPORATE SOURCE: CHU Clermont-Ferrand, Pulmonary Department, Hopital G Montpied, Clermont-Ferrand, Fr.
SOURCE: International Journal of Chronic Obstructive Pulmonary Disease (2007), 2(4), 559-565
CODEN: IJCOC3; ISSN: 1176-9106
PUBLISHER: Dove Medical Press (NZ) Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This was a multicenter, randomized, double-blind within device, parallel-group, dose-ranging study. COPD patients (n = 202; 86% male; mean age: 61 years) were randomized to receive **tiotropium** 1.25 μg, 2.5 μg, 5 μg, 10 μg, or 20 μg Respimat SMI (a novel, propellant-free device); **tiotropium** 18 μg HandiHaler; placebo Respimat; or placebo HandiHaler for 3 wk. The primary endpoint was trough FEV1 on Day 21. Other assessments included FVC, PEFR, rescue medication use, safety, and pharmacokinetics. In general, all active treatments improved the primary and secondary endpoints on Day 21 (steady state) compared with placebo. **Tiotropium** 5 μg Respimar, 20 μg Respimat, and **tiotropium** 18 μg HandiHaler were statistically significantly higher than placebo for the primary endpoint (mean change in trough FEV1 was 150 mL (both Respimat doses) vs. 20 mL (placebo Respimat); $p < 0.05$; and 230 mL (HandiHaler) vs. -90 mL (placebo HandiHaler); $p \leq 0.001$). The **urinary** excretion (up to 2 h post-dose) of **tiotropium** 5-10 μg Respimat was comparable with **tiotropium** 18 μg HandiHaler; the overall incidence of adverse events was comparable across treatment groups. **Tiotropium** 5 and 10 μg Respimar improve lung function in COPD patients and appear to be comparable with **tiotropium** 18 μg HandiHaler.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:324265 CAPLUS
TITLE: Safety, tolerability and risk benefit analysis of **tiotropium** in COPD
AUTHOR(S): Oba, Yuji; Zaza, Tareq; Thameem, Danish M.
CORPORATE SOURCE: School of Medicine, Division of Pulmonary, Critical Care and Environmental Medicine, University of Missouri, Columbia, MO, USA
SOURCE: International Journal of Chronic Obstructive Pulmonary Disease (2008), 3(4), 575-584
CODEN: IJCOC3; ISSN: 1178-2005
PUBLISHER: Dove Medical Press (NZ) Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB COPD is a chronic disease and, like many other chronic diseases, there is no treatment to reverse the severity of the disease except for lung transplant. To date, no inhaled medications have been shown to improve survival. **Tiotropium bromide** is a long-acting inhaled anticholinergic drug for the treatment of COPD that can improve lung function, reduce symptoms and exacerbations, and improve quality of life with once-daily dosing. It was initially approved and marketed in several countries in Europe in 2002 and then approved in the US in 2004. **Tiotropium** is generally well tolerated with dry mouth being the main adverse effect. Other adverse effects include constipation, tachycardia, blurred vision, **urinary** retention and increased intraocular pressure. Despite the recently raised concerns about an excess risk of cardiovascular adverse events with inhaled anticholinergic agents, the risk/benefit ratio of **tiotropium** appears still favorable given the favorable safety profile demonstrated in the UPLIFT study. However, caution should be advised in patients at high risk for cardiovascular disease given the paucity of data in such patients.
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:71091 CAPLUS
DOCUMENT NUMBER: 142:162623
TITLE: Medicinal compositions containing tricyclic heterocyclic compound and anticholinergic agent
INVENTOR(S): Yamagata, Tsuyoshi; Shirakura, Shiro
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007191	A1	20050127	WO 2004-JP10521	20040716
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,				

SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2532805	A1	20050127	CA 2004-2532805	20040716
EP 1652532	A1	20060503	EP 2004-747885	20040716
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
US 20060160887	A1	20060720	US 2005-562635	20051229
PRIORITY APPLN. INFO.:			JP 2003-197662	A 20030716
			WO 2004-JP10521	W 20040716

AB It is intended to provide a medicinal composition useful in treating, for example, hyperactive **bladder** which comprises 3,3,3-trifluoro-2-hydroxy-2-methyl-N-(5,5,10-trioxo-4,10-dihydrothieno[3,2-c][1]benzothiepin-9-yl)propanamide or a pharmacol. acceptable salt thereof and an anticholine drug. The effect of combination of (S)-(+)-3,3,3-trifluoro-2-hydroxy-2-methyl-N-(5,5,10-trioxo-4,10-dihydrothieno[3,2-c][1]benzothiepin-9-yl)propanamide 0.01 and tolterodine 3 mg/kg on **bladder** contraction in spinal cord injury rats was examined

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:506580 CAPLUS
DOCUMENT NUMBER: 139:79178
TITLE: Synthesis of 3H-pyrrolo[2,3-d]pyrimidine derivatives and use as phosphodiesterase VII inhibitors and in combination with other agents
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent GmbH, Germany
SOURCE: Ger. Offen., 36 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10163991	A1	20030703	DE 2001-10163991	20011224
CA 2471538	A1	20030710	CA 2002-2471538	20021108
WO 2003055882	A1	20030710	WO 2002-EP12533	20021108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002367090	A1	20030715	AU 2002-367090	20021108
AU 2002367090	B2	20081113		
EP 1458722	A1	20040922	EP 2002-805744	20021108
EP 1458722	B1	20081015		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
BR 2002015308	A	20041221	BR 2002-15308	20021108
HU 2004002216	A2	20050228	HU 2004-2216	20021108
CN 1608067	A	20050420	CN 2002-826034	20021108
JP 2005520801	T	20050714	JP 2003-556412	20021108

AT 411316	T	20081015	AT 2002-805744		20021108
ES 2314132	T3	20090316	ES 2002-805744		20021108
MX 2004006235	A	20041101	MX 2004-6235		20040623
US 20050059686	A1	20050317	US 2004-500040		20040623
US 7498334	B2	20090303			
ZA 2004005859	A	20050517	ZA 2004-5859		20040722
PRIORITY APPLN. INFO.:			DE 2001-10163991	A	20011224
			WO 2002-EP12533	W	20021108

OTHER SOURCE(S): MARPAT 139:79178

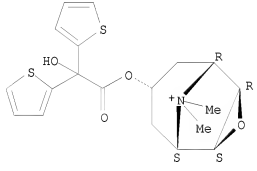
AB The invention concerns the synthesis of 3H-pyrrolo[2,3-d]pyrimidine derivs., their physiol. acceptable salts, stereoisomers, solvates, mixts. thereof and their use as phosphodiesterase VII inhibitors in the treatment of diseases that are influenced by the phosphodiesterase VII regulation of human eosinophil activation and degranulation. Osteoporesis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, AIDS, autoimmune and heart diseases can be treated with the drugs. Thus the synthesis of 5-isopropyl-4-oxo-7-p-tolyl-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidine-6-carboxylic acid Et ester and analog compds. is described along with injection, suppository, tablet and other formulations.

IT **136310-93-5, Tiotropium bromide**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthesis of 3H-pyrrolo[2,3-d]pyrimidine derivs. and use as phosphodiesterase VII inhibitors and in combination with other agents)

RN 136310-93-5 CAPLUS

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



● Br⁻

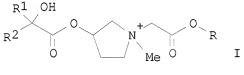
L8 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2007:565400 CAPLUS
DOCUMENT NUMBER:	147:10090
TITLE:	Quaternary ammonium derivatives as soft anticholinergic esters
INVENTOR(S):	Bodor, Nicholas S.
PATENT ASSIGNEE(S):	Bodor, Nicholas, S., USA
SOURCE:	PCT Int. Appl., 126 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007058971	A2	20070524	WO 2006-US43858	20061113
WO 2007058971	A3	20070726		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW		
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA		
AU 2006315657	A1	20070524	AU 2006-315657	20061113
CA 2627982	A1	20070524	CA 2006-2627982	20061113
US 20070123557	A1	20070531	US 2006-598079	20061113
US 7399861	B2	20080715		
EP 1948596	A2	20080730	EP 2006-837367	20061113
R:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR			
US 20080242651	A1	20081002	US 2008-137896	20080612
US 20090075954	A1	20090319	US 2008-138013	20080612
PRIORITY APPLN. INFO.:			US 2005-735207P	P 20051110
			US 2005-735206P	P 20051110
			US 2006-598076	A3 20061113
			US 2006-598079	A3 20061113
			WO 2006-US43858	W 20061113

OTHER SOURCE(S): MARPAT 147:10090
GI



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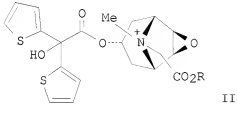


II

AB Soft anticholinergic esters I·X- [R1, R2 = both Ph or one is Ph and the other is cyclopentyl; R = straight or branched C1-8-alkyl; X" = anion with a single neg. charge (Cl, Br, I, sulfate, SO3Me, NO3, maleate, OAc, citrate, fumarate, tartrate, oxalate, succinate, benzoate, OTs)] or

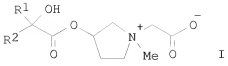
II·X- said compds. having the R, S or RS stereoisomeric configuration at each chiral center unless specified otherwise, or being a mixture thereof are described. Thus, 3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(methoxycarbonylmethyl)-1-methylpyrrolidinium bromide [I; R1 = cyclopentyl, R2 = PH, R = Me, X = Br] was prepared from PhCOCO2H via Grignard reaction with cyclopentylmagnesium bromide in Et2O, esterification with MeI in DMF containing K2CO3, transesterification with N-methyl-3-pyrrolidinol in hepaten to which sodium was added, and quaternization with BrCH2CO2Me. The anticholinergic activity of I [R1 = cyclopentyl, R2 = Ph, R = Me, X = Br] was determined [pKi = 7.91 vs. muscarinic receptor M1; pKi = 7.79 vs. muscarinic receptor M2; pKi = 7.80 vs. muscarinic receptor M3; pKi = 8.29 vs. muscarinic receptor M4; pA2 = 7.9 for ileum contractions].

L8 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:564522 CAPLUS
DOCUMENT NUMBER: 147:10089
TITLE: Quaternary ammonium derivatives as soft anticholinergic zwitterions
INVENTOR(S): Bodor, Nicholas S.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 117pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007059021	A1	20070524	WO 2006-US43966	20061113
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20070123557	A1	20070531	US 2006-598079	20061113
US 7399861	B2	20080715		
US 20080027091	A1	20080131	US 2006-598076	20061113
US 7417147	B2	20080826		
EP 1957451	A1	20080820	EP 2006-837428	20061113
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
US 20080242651	A1	20081002	US 2008-137896	20080612

PRIORITY APPLN. INFO.:
US 2005-735206P P 20051110
US 2005-735207P P 20051110
US 2006-598076 A3 20061113
WO 2006-US43966 W 20061113

OTHER SOURCE(S): MARPAT 147:10089
GI



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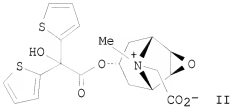


II

AB Soft anticholinergic zwitterions I [R1, R2 = both Ph or one is Ph and the other is cyclopentyl] or II said compds. having the R, S or RS stereoisomeric configuration at each chiral center unless specified otherwise, or being a mixture thereof are described. Thus, (±)-3-(2-cyclopentyl-2-phenyl-2-hydroxyacetoxy)-1-(carboxymethyl)-1-methylpyrrolidinium inner salt I [R1 = cyclopentyl, R2 = Ph] was prepared from PhCOCO2H via Grignard reaction with cyclopentylmagnesium bromide in Et2O, esterification with MeI in DMF containing K2CO3, transesterification with N-methyl-3-pyrrolidinol in heptane, quaternization with BrCH2CO2Me in MeCN and hydrolysis.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:20131 CAPLUS
DOCUMENT NUMBER: 148:346852
TITLE: Pharmacological analysis of the interaction of antimuscarinic drugs at M2 and M3 muscarinic receptors in vivo using the pithed rat assay
AUTHOR(S): Armstrong, Scott R.; Briones, Sergio; Horger, Brian; Richardson, Carrie L.; Jaw-Tsai, Sarah; Hegde, Sharath S.
CORPORATE SOURCE: Department of Pharmacology, Theravance, South San Francisco, CA, 94080, USA
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (2008), 376(5), 341-349
CODEN: NSAPCC; ISSN: 0028-1298
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Muscarinic receptor antagonists form the mainstay of the therapeutic options for airway, **bladder**, and gastrointestinal smooth muscle disorders. Both M2 and M3 muscarinic receptors are involved in mediating smooth muscle contractility, although the relative functional contribution of each subtype, especially in the disease state, is unclear. Because the potency and selectivity of compds. for a given receptor in an in vivo setting can be dissimilar to that observed in an in vitro system, we developed an in vivo assay to simultaneously determine the absolute potency and selectivity of muscarinic receptor antagonists at M2 and M3 receptors using the pithed rat. Methacholine (MCh)-induced bradycardia and depressor responses were used as surrogate functional endpoints for M2 and M3 receptor activation, resp. The influence of the muscarinic antagonists, tolterodine, oxybutynin, darifenacin, Ro 320-6206,

solifenacin, or **tiotropium** on the MCh-induced responses were studied. The estimated DR10 values (dose producing a tenfold shift in the MCh curve) of tolterodine, oxybutynin, darifenacin, Ro 320-6206, solifenacin, and **tiotropium** for the M2 muscarinic receptor-mediated bradycardia were 0.22, 1.18, .apprx.2.6, 0.025, 0.40, and 0.0026 mg/kg, resp., and 0.14, 0.18, 0.11, 3.0, 0.18, and 0.0017 mg/kg, resp., for the M3 muscarinic receptor-mediated depressor response. In a sep. set of expts., a single i.v. dose of **tiotropium** was administered before a MCh curve at 1, 3, 6, or 9 h to determine if **tiotropium** exhibited time-dependent selectivity for the M3 receptor as has been reported from in vitro studies. The results indicate a slight preference of **tiotropium** for the M3 receptor at later time points. The pithed rat assay may serve useful for elucidating the functional contribution of M2 and M3 receptors to the in vivo pharmacol. effects of antagonists in disease animal models.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:672983 CAPLUS
DOCUMENT NUMBER: 147:102152
TITLE: pharmacetical powder compositions for inhalation
INVENTOR(S): Mueller-Walz, Rudi
PATENT ASSIGNEE(S): Jagotec A.-G., Switz.
SOURCE: PCT Int. Appl., 30pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007068443	A1	20070621	WO 2006-EP11941	20061212
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2006326315	A1	20070621	AU 2006-326315	20061212
CA 2632831	A1	20070621	CA 2006-2632831	20061212
EP 1962797	A1	20080903	EP 2006-829526	20061212
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR				
NO 2008002488	A	20080529	NO 2008-2488	20080529
IN 2008DN04899	A	20080808	IN 2008-DN4899	20080606
CN 101325945	A	20081217	CN 2006-80046598	20080612
PRIORITY APPLN. INFO.:			GB 2005-25254 A	20051212
			WO 2006-EP11941 W	20061212

AB A pharmacol. powder for inhalation comprising fine particles of a drug and particles of a force-controlling agent, wherein the particles of the force-controlling agent are disposed on the surface of the active particles as either a particulate coating, or as a continuous or discontinuous film. The powder may further comprise particles of a

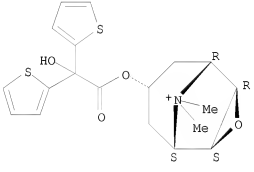
carrier material for supporting the drug particles. The force-controlling agent may be selected from: amino acids, peptides and polypeptides having a mol. weight of 0.25-1000 KDa, phospholipids, TiO2, Al3O2, SiO2, starch, and fatty acid salts. Also disclosed is a method of making such a powder for inhalation comprising mixing a force-controlling agent with particles of one or more pharmacol. active materials to obtain a mixture in which the particles of the force-controlling agent are disposed on the surface of the active particles as either a particulate coating, or as a continuous or discontinuous film. The mixing step may be achieved by sieving, mixing or blending, micronizing, and/or co-micronizing the particles of one or more pharmacol. active materials and particles of force-controlling agents. A powder formulation consisting of glycopyrrolate, magnesium stearate, and lactose monohydrate was obtained. The dry powder blend achieved is homogeneous and the blend has satisfying blend homogeneity.

IT **136310-93-5, Tiotropium bromide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical powder compns. for inhalation)

RN 136310-93-5 CAPLUS

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

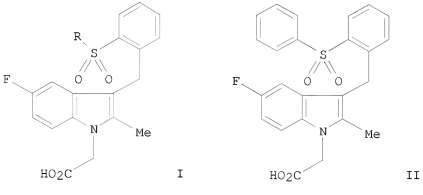
L8 ANSWER 13 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:123834 CAPLUS
DOCUMENT NUMBER: 148:183423
TITLE: Preparation of indole compounds having CRTH2 antagonist activity for treating allergic diseases, asthma, and inflammatory conditions
INVENTOR(S): Armer, Richard Edward; Wynne, Graham Michael
PATENT ASSIGNEE(S): Oxagen Limited, UK
SOURCE: PCT Int. Appl., 68pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2008012511	A1	20080131	WO 2007-GB2761	20070720
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2007279079	A1	20080131	AU 2007-279079	20070720
PRIORITY APPLN. INFO.:			GB 2006-14608	A 20060722
			GB 2006-24176	A 20061204
			WO 2007-GB2761	W 20070720

OTHER SOURCE(S): MARPAT 148:183423

GI



AB Compds. of general formula I (wherein R is Ph optionally substituted with one or more halo substituents) and their pharmaceutically acceptable salts, hydrates, solvates, complexes or prodrugs are antagonists at the CRTH2 receptor and are useful in the treatment of conditions mediated by PGD2 or other agonists binding to CRTH2. These include allergic diseases, asthmatic conditions and inflammatory diseases. A process for preparing I was addnl. claimed. Example compound II was prepared by reacting 2-(phenylsulfonyl)benzaldehyde with 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetic acid and saponification of the resulting ester. In an assay measuring inhibition of 13,14-dihydro-15-keto-prostaglandin D2 induced blood eosinophilia in rats, II had an ED50 of 0.0025 μg/mL.

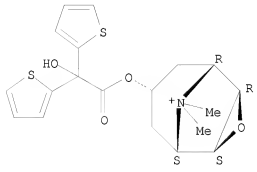
IT **136310-93-5, Tiotropium bromide**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(codrugs; preparation of indole compds. having CRTH2 antagonist activity for treating allergic diseases, asthma, inflammatory conditions, and other diseases)

RN 136310-93-5 CAPLUS

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane,

7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 14 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:376641 CAPLUS
DOCUMENT NUMBER: 138:385438
TITLE: Preparation of pyridazinylmethanoylphenylhydrazonomalonitriles as phosphodiesterase IV inhibitors.
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael; Beier, Norbert; Schelling, Pierre; Ehring, Thomas
PATENT ASSIGNEE(S): Merck Patent Gmbh, Germany
SOURCE: PCT Int. Appl., 114 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003039548	A1	20030515	WO 2002-EP11351	20021010
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2465746	A1	20030515	CA 2002-2465746	20021010
AU 2002363368	A1	20030519	AU 2002-363368	20021010
AU 2002363368	B2	20071213		
AU 2002363368	B9	20080124		
EP 1441730	A1	20040804	EP 2002-802625	20021010
EP 1441730	B1	20060809		

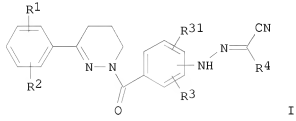
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

BR	2002013683	A	20041026	BR	2002-13683	20021010
HU	2004001747	A2	20050128	HU	2004-1747	20021010
HU	2004001747	A3	20050628			
CN	1585641	A	20050223	CN	2002-822216	20021010
JP	2005511595	T	20050428	JP	2003-541839	20021010
AT	335486	T	20060915	AT	2002-802625	20021010
ES	2268157	T3	20070316	ES	2002-802625	20021010
RU	2302412	C2	20070710	RU	2004-117171	20021010
MX	2004004263	A	20040708	MX	2004-4263	20040504
US	20040261190	A1	20041230	US	2004-494631	20040504
US	7141572	B2	20061128			
ZA	2004004387	A	20060222	ZA	2004-4387	20040603
US	20060270676	A1	20061130	US	2006-497235	20060802

PRIORITY APPLN. INFO.: EP 2001-125455 A 20011105
WO 2002-EP11351 W 20021010
US 2004-494631 A1 20040504

OTHER SOURCE(S): MARPAT 138:385438

GI



I

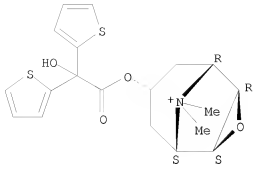
AB Title compds. [I; R1, R2 = H, OH, OR5, SR5, SOR5, SO2R5, X; R1R2 = OCH2O, OCH2CH2O; R3, R31 = H, R5, OH, OR5, NH2, NHR5, NHCOR5, X, CO2H, CO2R5, CONH2, etc.; R4 = cyano, tetrazolyl; R5 = (fluoro-substituted) A, cycloalkyl, (CH2)nAr; A = (fluoro- and/or chloro-substituted) alkyl, alkenyl; Ar = Ph; n = 0-2; X = F, Cl, Br, iodo], were prepared Thus, [3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazine-1-yl]-(3-aminophenyl)methanone (preparation given) was stirred with NaNO2 in aqueous HCl for 1 h at -2° to 0°; malononitrile in H2O was added followed by stirring for 2 h to give a residue which was treated with KOH in MeOH to give 2-[[3-[1-[3-(3,4-diethoxyphenyl)-5,6-dihydro-4H-pyridazin-1-yl]methanoyl]phenyl]hydrazono]malononitrile K salt. I were said to give a marked reduction of T cell proliferation. I are claimed for treatment of osteoporosis, tumors, cachexia, atherosclerosis, rheumatoid arthritis, multiple sclerosis, diabetes mellitus, inflammatory processes, allergies, asthma, autoimmune diseases, myocardial diseases, AIDS, etc.

IT **136310-93-5, Tiotropium bromide**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(coadministration; preparation of pyridazinylmethanoylphenylhydrazonomalonitriles as phosphodiesterase IV inhibitors)

RN 136310-93-5 CAPLUS

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 15 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:356269 CAPLUS
DOCUMENT NUMBER: 138:348761
TITLE: Type 4 phosphodiesterase inhibitors and therapeutic uses thereof
INVENTOR(S): Eggenweiler, Hans-Michael; Wolf, Michael
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003037349	A1	20030508	WO 2002-EP9596	20020828
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2462525	A1	20030508	CA 2002-2462525	20020828
AU 2002333730	A1	20030512	AU 2002-333730	20020828
EP 1463509	A1	20041006	EP 2002-802281	20020828
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
CN 1578665	A	20050209	CN 2002-821711	20020828
HU 2004001984	A2	20050228	HU 2004-1984	20020828
HU 2004001984	A3	20050628		
JP 2005515975	T	20050602	JP 2003-539692	20020828
MX 2004003668	A	20040722	MX 2004-3668	20040419
US 20040259863	A1	20041223	US 2004-494379	20040430
PRIORITY APPLN. INFO.:			EP 2001-125394 A	20011031
			WO 2002-EP9596 W	20020828

OTHER SOURCE(S): MARPAT 138:348761

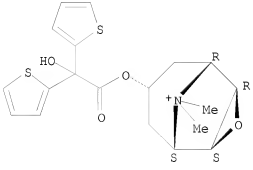
AB The invention discloses the use of type 4 phosphodiesterase inhibitors (PDE IV inhibitors) to treat diseases, as well as combinations of PDE IV inhibitors with other drugs.

IT **136310-93-5, ; Tiotropium bromide**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sphosphodiesterase IV inhibitors, therapeutic uses, and use with other agents)

RN 136310-93-5 CAPLUS

CN 3-Oxa-9-azoniatricyclo[3.3.1.02,4]nonane, 7-[(2-hydroxy-2,2-di-2-thienylacetyl)oxy]-9,9-dimethyl-, bromide (1:1), (1α,2β,4β,5α,7β)- (CA INDEX NAME)

Relative stereochemistry.



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REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 16 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2009:198480 CAPLUS

DOCUMENT NUMBER: 150:245316

TITLE: Drug combinations for the treatment of clozapine-induced sialorrhea

INVENTOR(S): Goldsmith, Paul; Roach, Alan Geoffrey

PATENT ASSIGNEE(S): Summit Corporation PLC, UK

SOURCE: PCT Int. Appl., 24pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009022096	A1	20090219	WO 2008-GB2650	20080804

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: GB 2007-15790 A 20070813

AB A combination comprises an α2-adrenoceptor agonist and an anti-muscarinic agent for the treatment or prevention of sialorrhoea, for example clozapine-induced sialorrhoea, in a patient subgroup selected from: (I) those suffering from, or at risk of suffering from: (a) a pathol. confused mental state; (b) hallucinations; (c) dementia, for example Lewy body dementia; (d) cognitive disturbances; (e) **bladder** outflow obstruction; (f) prostatism, for example benign prostatic hypertrophy or prostate cancer; (g) glaucoma; (h) hypotension; (i) somnolence; (j) ocular hypertension and (k) needle phobia; or (II) (a) individuals with cortical Lewy bodies; (b) males with an enlarged prostate; (c) individuals with a tendency to presyncope or syncope; (d) individuals with a score ≥ 1 on questions 1.1 and I.2 on the UPDRS or <88/100 on the Cambridge ACE (Addenbrooke's cognitive assessment); (e) individuals with a score ≥ 1 on American Urol. Association symptom index; (f) individuals with an intraocular pressure of >20 mmHg or taking medication to lower previously raised intraocular pressure; (g) individuals with needle phobia; (h) individuals with a score 1 on Q42 on section C of the UPDRS (unified Parkinson's disease rating scale); (i) individuals with a score 1 on Q41 on section C of the UPDRS; (j) individuals with an ESS (Epworth sleepiness score) of >10; and (k) individuals with a leaky blood brain barrier. Thus, a reduction in saliva production following administration of oxybutynin and clonidine was observed in healthy male volunteers.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 17 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:1088475 CAPLUS

DOCUMENT NUMBER: 147:398640

TITLE: M3 muscarinic receptor antagonists for treatment of M3 muscarinic receptor-expressing tumors

INVENTOR(S): Spindel, Eliot R.; Sekhon, Harmanjatinder; Song, Pingfang

PATENT ASSIGNEE(S): Oregon Health & Science University, USA

SOURCE: PCT Int. Appl., 51pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007109142	A2	20070927	WO 2007-US6658	20070316
WO 2007109142	A3	20071206		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW,

GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

US 20090062326 A1 20090305 US 2008-281976 20080905
PRIORITY APPLN. INFO.: US 2006-783461P P 20060317
WO 2007-US6658 W 20070316

AB The invention discloses methods for treating a tumor using M3 muscarinic receptor antagonists, e.g. darifenacin. In some examples, the tumor expresses M3 muscarinic receptors, e.g. tumors associated with smoking. The invention also discloses compns. that can be used to practice such methods.

L8 ANSWER 18 OF 18 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:143401 CAPLUS
DOCUMENT NUMBER: 150:191323
TITLE: Substituted indoles as cysteinyl leukotriene receptor modulators and their preparation and use in the treatment of diseases
INVENTOR(S): Gant, Thomas G.; Sarshar, Sepehr
PATENT ASSIGNEE(S): Auspex Pharamaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 107pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009018280	A2	20090205	WO 2008-US71482	20080729

W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2007-952862P P 20070730
OTHER SOURCE(S): MARPAT 150:191323
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Disclosed herein are substituted indole cysteinyl leukotriene receptor modulators of formula I, process of preparation threof, pharmaceutical compns. thereof, and methods of use thereof. Example compound I wherein R1 - R33 are independently H and D, with the proviso that at least one of R1 - R33 is D; and pharmaceutically acceptable salts thereof, are claimed. Example compound II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their cysteinyl leukotriene receptor modulatory activity (some data given).

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